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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,165	07/26/2002	Paul B. Fisher	34585-A-PCT/USA070050.166	4970

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,165	FISHER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-17,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-26-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group II, claims 9, 10 and 18, in the reply filed on 6-17-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-8, 11-17, 19 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6-17-04.

Claims 1-20 are pending and claims 9, 10 and 18 are under consideration.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to **a single paragraph on a separate sheet within the range of 50 to 150 words**. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract filed 9-21-01 is improper because it is the front page of WO 00/55310. The abstract should be **a single paragraph on a separate sheet within the range of 50 to 150 words**. Appropriate correction is required.

Claim Objections

4. Claims 9 and 10 are objected to because of the following informalities: Claims 9 and 10 depend on claim 1, which is non-elected invention. Changing claim 9 to independent claim and including the limitations of claim 1 would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9 and 10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 9 and 10 are directed to a non-human transgenic animal, such as a transgenic mouse, comprising a vector having a nucleic acid encoding a tetracycline controlled transactivator under the control of a human EF-1 alpha promoter, a tetracycline inducible operator binding element and a gene of interest.

The specification teaches making a transgenic mouse via microinjection of pEF1prtTA vector into pronuclei of fertilized mouse eggs and implanted said fertilized eggs into pseudo-pregnant female mice. The specification discloses the establishment of a female founder mouse and the F1 generation, and 8 out of 15 F1 generation mice were tested positive for the transgene (see specification, p. 20-21). The specification indicates that the transgenic mice can be used to study the in vivo effect of specific genes in animals or screen for anti-tumoral or other pharmacological effects of drugs or small molecules (specification, p. 21).

The specification fails to provide a specific and substantial utility or a well-established utility for the claimed transgenic non-human animals. No phenotype of the claimed transgenic non-human animals has been disclosed. The specification also fails to identify what disease or disorder is associated with the claimed transgenic non-human animals. There is no correlation between a phenotype of the claimed transgenic non-human animals and a particular disease or disorder. Therefore, the specification fails to provide an asserted specific utility for the claimed transgenic non-human animals.

A substantial utility is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, basic research for studying the properties of a claimed product, a method of treating an unspecified disease or condition, and a method of assaying for or identifying a material that itself has "no specific and/or substantial utility" do not define "substantial utilities". Uses of the claimed transgenic non-human animal as an animal model to study effects of specific genes in animal, or to screen for anti-tumoral or other pharmacological effects of drugs or small molecules, are not considered substantial utilities because these uses do not define a "real world" use. As discussed above, no phenotype of the claimed transgenic non-human animals has been disclosed and there is no correlation between a phenotype of the claimed transgenic non-human animals and a particular disease or disorder. Absent the phenotype of the claimed transgenic non-human animal and the correlation between a phenotype of the claimed transgenic non-human animal, such as a transgenic mouse, and a particular disease or disorder, no "real world" use of the claimed transgenic non-human animal

could be established. Thus, the specification fails to support and provide evidence for a specific and substantial utility or a well-established utility of the claimed transgenic non-human animals.

Further, claims 9 and 10 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Although claim 1 is non-elected invention, since claims 9 and 10 depend on claim 1, the following indefiniteness of claim 1 is still discussed.

The phrase "a tetracycline inducible operator binding element under the control of the nucleic acid encoding the transactivator" on lines 7-9 of claim 1 is vague and renders the claim indefinite. The nucleic acid encoding the transactivator is a coding sequence. It is unclear how a coding sequence could control a tetracycline inducible operator binding element.

The phrase "gene of interest under the control of the promoter" on line 10 of claim 1 is vague and renders the claim indefinite. It is unclear whether "the promoter" is the human EF-1 alpha promoter that control the expression of the tetracycline controlled transactivator or it is a

second copy of the human EF-1 alpha promoter. It is also unclear where the gene of interest is located within the vector.

Claims 9 and 10 are indefinite because they depend on claim 1, which is non-elected invention, but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 9, 10 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9, 10 and 18 are directed to a non-human transgenic animal, such as a transgenic mouse, comprising a vector having a nucleic acid encoding a tetracycline controlled transactivator under the control of a human EF-1 alpha promoter, a tetracycline inducible operator binding element and a gene of interest, a method of using said transgenic non-human animal for screening anti-tumor drug.

The claims read on transgenic non-human animals comprising the claimed vector. The claims encompass numerous homozygous or heterozygous transgenic non-human animals derived from various species, such as mice, rats, pigs, cows, sheep, rabbits, whales, insects,

arthropods, fishes etc., with unknown and unidentified phenotypes. The specification only discloses the making of founder and F1 generation of transgenic mice comprising the vector pEF1prtTA. The specification fails to disclose the structural feature or phenotype of the claimed transgenic non-human animals. The phenotypes of various heterozygous or homozygous transgenic non-human animals having the claimed vector were unpredictable at the time of the invention. The structural features and phenotypes of the transgenic non-human animals that can distinguish said transgenic non-human animals from wild-type animals have not been disclosed. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify the claimed transgenic non-human animals, and because the claimed transgenic non-human animals are highly various, the disclosure in the present application is insufficient to describe the claimed transgenic non-human animals.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed transgenic non-human animals. Thus, it is concluded that the written description requirement is not satisfied for the transgenic non-human animals as claimed.

4. Claims 9, 10 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 9, 10 and 18 are directed to a non-human transgenic animal, such as a transgenic mouse, comprising a vector having a nucleic acid encoding a tetracycline controlled transactivator under the control of a human EF-1 alpha promoter, a tetracycline inducible operator binding element and a gene of interest, a method of using said transgenic non-human animal for screening anti-tumor drug.

The claims read on transgenic non-human animals comprising the claimed vector. The claims encompass numerous homozygous or heterozygous transgenic non-human animals derived from various species, such as mice, rats, pigs, cows, sheep, rabbits, whales, insects, arthropods, fishes etc., with unknown and unidentified phenotypes. The specification teaches making a transgenic mouse via microinjection of pEF1prtTA vector into pronuclei of fertilized mouse eggs and implanted said fertilized eggs into pseudo-pregnant female mice. The specification discloses the establishment of a female founder mouse and the F1 generation, and 8 out of 15 F1 generation mice were tested positive for the transgene (see specification, p. 20-21).

The specification fails to disclose the structural features or phenotypes of the claimed transgenic non-human animals. The specification fails to provide adequate guidance and evidence for the production of numerous heterozygous or homozygous transgenic non-human animals, which have their phenotypes that are distinguishable from corresponding wild type animals.

The state of the art in the fields of transgenic animal, including knockout and knock-in animals, at the time of the invention was unpredictable, the transgene expression and resulting phenotype of such expression is not always accurately predictable. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest,

promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Sigmund, June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

In addition, Wolfer et al., 2002 (Trends in Neurosciences, Vol. 25, No. 7, p. 336-340) points out that flanking-gene or linkage disequilibrium problem exists in producing knockout mice having null mutation due to the use of ES cells derived from 129 INBRED mice and its crossing with C57BL6 mice, and "the phenotype resulting from a null mutation can depend on the general genetic background of mouse strains used for this research. Thus, congenic strains carrying the same null mutation can sometimes show widely divergent phenotypes, depending on the genotype of the recipient strain" (e.g. p. 326). Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). Gene replacement by homologous recombinantion in

somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so-called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column).

In view of the inherent unpredictability of the resulting phenotypes of the claimed transgenic animals, the lack of evidence for the phenotypes of the claimed transgenic non-human animals, and the limitation of the use of ES cells for generating transgenic animals, one skilled in the art at the time of the invention would not know how to use the claimed transgenic non-human animals with unknown phenotypes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

5. Claims 9, 10 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of the use of transgenic non-human animals. Since the preparations of transgenic non-human animals are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the preparations of transgenic non-human animals are not so obtainable or available, the requirements of 35 U.S.C. § 112, regarding "how to make", may be satisfied by a deposit of the transgenic non-human animals. The specification does not disclose a repeatable process to obtain the claimed transgenic non-human animals and it is not apparent if these are readily available to the public. It is noted that there is no indication in the specification as to public availability. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific transgenic non-human animal lines have been deposited under the Budapest Treaty and that the lines will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become unviable.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are

available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER